SYNTHESES IN THE FIELD OF QUINOLINE DERIVATIVES

V. Synthesis of 8-Hydroxyquinolin-5-ylmethyl Acrylate and Methacrylate*

G. K. Kirienko, L. I. Aristov, and A. A. Shamshurin

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The reaction of potassium acrylate and methacrylate with the hydrochloride of 5-chloromethylquinolin-8-ol has given the corresponding hydroxyquinolinylmethyl esters.

Recently, increased interest has arisen in biologically active polymeric materials and preparations [2–5]. One of the methods for obtaining such substances may be the copolymerization of monomers possessing a given physiological activity.

We have investigated the synthesis of monomers from potassium acrylate and methacrylate (II) and 5-chloromethylquinolin-8-ol hydrochloride (I) according to the following stoichiometric equations:

$$\underset{\text{I}}{\text{HCl}\cdot\text{RCH}_2\text{Cl}}+\underset{\text{II}}{\text{KOCOCH}=\text{CH}_2}\longrightarrow \longrightarrow \underset{\text{III}}{\text{HCl}\cdot\text{RCH}_2\text{OCOCH}=\text{CH}_2}+\text{KCl}, \quad (1)$$

$$\underset{\text{I}}{\text{HCl}\cdot\text{RCH}_2\text{Cl}}+\underset{\text{II}}{\text{KOCOCH}=\text{CH}_2}+(\text{KH, NaH, K}_2)\text{CO}_3\longrightarrow \longrightarrow \underset{\text{III}}{\text{RCH}_2\text{OCOCH}=\text{CH}_2}+2\text{KCl(KCl, NaCl)}+\text{H}_2\text{O}+\text{CO}_2, \quad (2)$$

$$\underset{\text{I}}{\text{HCl}\cdot\text{RCH}_2\text{Cl}}+\underset{\text{II}}{2\text{KOCOCH}=\text{CH}_2}\longrightarrow \longrightarrow \underset{\text{III}}{\text{RCH}_2\text{OCOCH}=\text{CH}_2}+2\text{KCl}+\text{HOCOCH}=\text{CH}_2, \quad (3)$$

The preparation of monomers with a quinolin-8-ol residue is of interest, since quinolin-8-ol itself and a number of its derivatives possess considerable bactericidal, antiamebal, and fungicidal properties [6, 7].

The nature of the solvent proved to have a considerable influence on the yield of the final products III. A number of aprotic solvents (petroleum ether, benzene, ethyl acetate) were tested. The best yields of esters by reaction (1) were obtained in ethyl acetate (30%), while in petroleum ether and benzene the yield of III did not exceed 14%. When hydrogen chloride acceptors were used (2), the yields of esters could be raised to 55%, but in this case the nature of the solvent and of the hydrogen chloride acceptors had a considerable influence on the course of the reaction, as Table 1 shows. The data on the kinetics of the evolution of CO_2 were treated by the method of least squares [8].

In a blank experiment, the reaction between I and an acceptor (with respect to the evolution of CO_2) obeyed a first-order equation with a rate constant of $1.7 \cdot 10^{-6}$ *l*/mole · sec; the constant for a given type of acceptor was the same in petroleum ether and in ethyl acetate. In the presence of potassium salts of acids, the nature of the solvent, the type of acceptor, and the salt of the acid taken proved to have a considerable influence on the rate constant of the evolution of CO_2 (see Table 1).

Since we could not obtain a greater yield of esters by reaction (2) than 55%, we used variant (3). In this case the esters were obtained with a yield of 60%, as can be seen from the figures of Table 2.

It has been shown in a number of papers and reviews that the nature of the solvent sometimes has a decisive influence on the favorable outcome of a reaction [9–11]. Our experimental data are in full agreement with this.

In 5-chloromethylquinolin-8-ol hydrochloride, because of the combined actions of the negative inductive effect of the chlorine atom of the chloromethyl group and the positive mesomeric effect of the hydroxyl group, this chlorine atom and the CH_2Cl group itself possess a high mobility. This is confirmed by the impossibility of obtaining free 5-chloromethylquinolin-8-ol without its conversion into the carbinol [12], and also by the ease of elimination of the CH_2OH group in the bromination reaction [13]. This may explain why, in a number of solvents (especially those with a high dielectric constant) the reaction takes place with the partial splitting off of the CH_2Cl group and with the predominant formation of bishydroxyquinolylmethane.

Syntheses by reaction (1) are practically complete after one hour (the yield of esters does not rise when the reaction time is increased). For the initial reactant I to take part in the reaction, it must be dissociated into ions. Consequently, solvents with high dielectric constants, which form complexes of the electron-donor or coordination type with the reactant or the substrate, generally favor the reaction. In our case, the most suitable solvent with specific solvation proved to be ethyl acetate. Because of the unshared pair of electrons on the oxygen atom, this solvent is capable of an electron-donating interaction both with the RCH_2^+ ion and with the cation of the substrate. This probably facilitates the cleavage of the corresponding ion pair with the formation of separate ions. In other solvents (benzene, toluene, petroleum ether), no such specific solvation is observed, which leads to low yields of the final products. Dimethylformamide proved to be unsuitable because of its condensation with the initial reactant, which has been observed earlier in the preparation of the corresponding ethers [12].

We have studied the IR spectra of the compounds obtained (recorded in KBr tablets on a UR-10 instrument). The spectrum of the acrylate (figure) shows

*For part IV, see [1].

Table 1

Synthesis* of 8-Hydroxyquinolin-5-ylmethyl Acrylate and Methacrylate in the Presence of Hydrogen Chloride Acceptors

Solvent**	Hydrogen chloride acceptor	K*** X 10^{-6} l/mole · sec	Amount of CO_2 liberated after 50 min, ml	Yield, %		
				esters III	bishydroxyquinolinylmethane (IV)	5-hydroxymethylquinolin-8-ol (V)
			Potassium acrylate			
A	$KHCO_3$	2.2	100	14	30	12
„	$NaHCO_3$	1.6	45	14	26	15
„	K_2CO_3	3.3	73	14	30	12
B	$KHCO_3$	1.6	100	37	20	—
„	$NaHCO_3$	5.0	100	55	17	—
„	K_2CO_3	8.3	73	33	24	—
C	$KHCO_3$	3.3	55	10	40	—
D	$KHCO_3$	11	100	—	35	15
			Potassium methacrylate			
A	$KHCO_3$	0.8	28	7	—	68
„	$NaHCO_3$	0.8	33	14	5	55
„	K_2CO_3	1.6	45	8	26	17
B	$KHCO_3$	1.4	45	15	11	17
„	$NaHCO_3$	1.4	78	27	5	45
„	K_2CO_3	1.4	68	34	10	17

*Equation (2)

**A is petroleum ether, bp 70–100° C; B is ethyl acetate, bp 77° C, ε 6.02, $\tilde{\mu}$ 1.81 D; C is nitromethane, bp 101° C, ε 35.9, μ 3.17 D; D is acetone, bp 56° C: ε 20.7, μ 2.2 D.

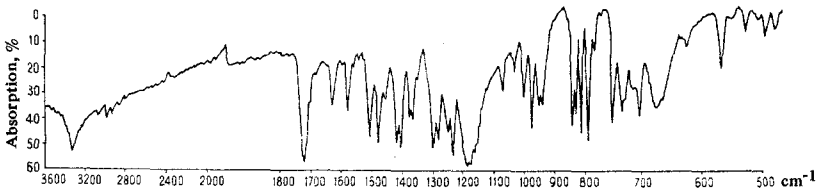
***Rate constant of the evolution of CO_2.

Table 2

Yields of 8-Hydroxyquinolin-5-ylmethyl Acrylate (HQA) and Methacrylate (HQM) as Functions of the Nature of the Solvent*

Solvent	Yield, %	
	HQA	HQM
Petroleum ether	14	25
Ethyl acetate	60	60
Benzene	22	40
Nitromethane	12	15

*Equation (3).



IR spectrum of 8-hydroxyquinolin-5-ylmethyl acrylate

bands characteristic for the quinoline ring (712, 1230, 1280, 1295, 1370, 1410, 1480, 1505, 1580, 1630, 3320 cm^{-1}) and also a band at 1720 cm^{-1} which is characteristic for the stretching vibrations of a C=O group in aryl esters and unsaturated esters; the characteristic group for the C—O bond at 1250 cm^{-1} appears with a low intensity. Other bands appear at 790 and 840 cm^{-1} which are not present in the spectrum of quinolin-8-ol. It is possible that these must be assigned to the C—C skeletal vibrations of an unsaturated chain [14].

EXPERIMENTAL

8-Hydroxyquinolin-5-ylmethyl acrylate. A flask was charged with a ground mixture consisting of 2.31 g (0.01 mole) of 5-chloromethylquinolin-8-ol hydrochloride, 1.0 g (0.01 mole) of potassium acrylate, and 1.0 g (0.01 mole) of potassium bicarbonate, and then 20 ml of ethyl acetate was added. The flask was connected via a reflux condenser with a burette for measuring carbon dioxide. Then it was heated in the boiling water bath for ~50 min until the evolution of carbon dioxide had practically ceased. After this, the solvent was filtered from the precipitate and the filtrate was distilled (in the case of high-boiling solvents, in vacuum). The product obtained, with mp 92–95° C, was recrystallized from petroleum ether. Colorless crystals, mp 95–96° C, readily soluble in benzene and ethyl acetate; yield 37%. C 67.92; H 5.04; N 6.19. Calculated for $C_{13}H_{11}NO_3$, %: C 68.10; H 4.80; N 6.11. The precipitate was added to acidified water and the mixture was neutralized with dilute ammonia solution. A mixture of products deposited which consisted of 5-hydroxymethylquinolin-8-ol (IV) and bishydroxyquinolinylmethane (V). After drying, this mixture was treated with ethyl ether in which IV is soluble and V is insoluble. The pure products, after recrystallization (IV from benzene and V from dimethylformamide) melted at 138–139° C and 279–281° C, respectively.

8-Hydroxyquinolin-5-ylmethylmethacrylate was obtained similarly; colorless crystals, mp 129–130° C, readily soluble in benzene and ethyl acetate. Found, %: C 69.25; H 5.31; N 5.88. Calculated for $C_{14}H_{13}NO_3$, %: C 69.13; H 5.35; N 5.76. The yields of the desired products and of the by-products when the reaction was carried out in accordance with Equations 2 and 3 are shown, respectively, in Tables 1 and 2.

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Institute of Chemistry AS Moldavian SSR, Kishinev